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**PROVISIONAL APPLICATION COVER SHEET**

This is a request for filing a PROVISIONAL APPLICATION for PATENT under 37 CFR 1.53(c).

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<b>TITLE OF THE INVENTION (280 characters max)</b> <b>INHIBITORS OF AKT ACTIVITY</b>			
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<b>ENCLOSED APPLICATION PARTS (check all that apply)</b>			
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Respectfully submitted,  
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Date:

Registration No.:

**August 6, 2003**  
**33,870**

☐ Additional inventors are being named on separately numbered sheets attached hereto.

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# INHIBITORS OF AKT ACTIVITY

## FIELD OF THE INVENTION

This invention relates to novel 1H-imidazo[4,5-c]pyridin-2-yl compounds, the  
 5 use of such compounds as inhibitors of PKB/AKT kinase activity and in the  
 treatment of cancer and arthritis.

## BACKGROUND OF THE INVENTION

The present invention relates to 1H-imidazo[4,5-c]pyridin-2-yl containing  
 10 compounds that are inhibitors of the activity of one or more of the isoforms of the  
 serine/threonine kinase, Akt (also known as PKB). The present invention also  
 relates to pharmaceutical compositions comprising such compounds and methods  
 of using the instant compounds in the treatment of cancer and arthritis.

Apoptosis (programmed cell death) plays essential roles in embryonic  
 15 development and pathogenesis of various diseases, such as degenerative neuronal  
 diseases, cardiovascular diseases and cancer. Recent work has led to the identifi-  
 cation of various pro- and anti-apoptotic gene products that are involved in the  
 regulation or execution of programmed cell death. Expression of anti-apoptotic  
 genes, such as Bcl2 or Bcl-x<sub>L</sub>, inhibits apoptotic cell death induced by various  
 20 stimuli. On the other hand, expression of pro-apoptotic genes, such as Bax or Bad,  
 leads to programmed cell death (Aams et al. *Science*, 281:1322-1326 (1998)). The  
 execution of programmed cell death is mediated by caspase -1 related proteinases,  
 including caspase-3, caspase- 7, caspase-8 and caspase-9 etc (Thornberry et al.  
*Science*, 281:1312-1316 (1998)).

The phosphatidylinositol 3'-OH kinase (PI3K)/Akt/PKB pathway appears  
 25 important for regulating cell survival/cell death (Kulik et al. *Mol.Cell.Biol.* 17:1595-  
 1606 (1997); Franke et al, *Cell*, 88:435-437 (1997); Kauffmann-Zeh et al. *Nature*  
 385:544-548 (1997) Hemmings *Science*, 275:628-630 (1997); Dudek et al.,  
*Science*, 275:661-665 (1997)). Survival factors, such as platelet derived growth  
 30 factor (PDGF), nerve growth factor (NGF) and insulin-like growth factor-1 (IGF-I),  
 promote cell survival under various conditions by inducing the activity of PI3K (Kulik  
 et al. 1997, Hemmings 1997). Activated PI3K leads to the production of  
 phosphatidylinositol (3,4,5)-triphosphate (PtdIns (3,4,5)-P3), which in turn binds to,  
 and promotes the activation of, the serine/ threonine kinase Akt, which contains a  
 35 pleckstrin homology (PH)-domain (Franke et al *Cell*, 81:727-736 (1995); Hemmings  
*Science*, 277:534 (1997); Downward, *Curr. Opin. Cell Biol.* 10:262-267 (1998),  
 Alessi et al., *EMBO J.* 15: 6541-6551 (1996)). Specific inhibitors of PI3K or



dominant negative Akt/PKB mutants abolish survival-promoting activities of these growth factors or cytokines. It has been previously disclosed that inhibitors of PI3K (LY294002 or wortmannin) blocked the activation of Akt/PKB by upstream kinases. In addition, introduction of constitutively active PI3K or Akt/PKB mutants promotes  
 5 cell survival under conditions in which cells normally undergo apoptotic cell death (Kulik et al. 1997, Dudek et al. 1997).

Analysis of Akt levels in human tumors showed that Akt2 is overexpressed in a significant number of ovarian (J. Q. Cheung et al. *Proc. Natl. Acad. Sci. U.S.A.* 89:9267-9271(1992)) and pancreatic cancers (J. Q. Cheung et al. *Proc. Natl. Acad. Sci. U.S.A.* 93:3636-3641 (1996)). Similarly, Akt3 was found to be overexpressed  
 10 in breast and prostate cancer cell lines (Nakatani et al. *J. Biol.Chem.* 274:21528-21532 (1999)).

The tumor suppressor PTEN, a protein and lipid phosphatase that specifically removes the 3' phosphate of PtdIns(3,4,5)-P3, is a negative regulator of the PI3K/Akt pathway (Li et al. *Science* 275:1943-1947 (1997), Stambolic et al. *Cell* 95:29-39 (1998), Sun et al. *Proc. Natl. Acad. Sci. U.S.A.* 96:6199-6204 (1999)).  
 15 Germline mutations of PTEN are responsible for human cancer syndromes such as Cowden disease (Liaw et al. *Nature Genetics* 16:64-67 (1997)). PTEN is deleted in a large percentage of human tumors and tumor cell lines without functional PTEN  
 20 show elevated levels of activated Akt (Li et al. supra, Guldberg et al. *Cancer Research* 57:3660-3663 (1997), Risinger et al. *Cancer Research* 57:4736-4738 (1997)).

These observations demonstrate that the PI3K/Akt pathway plays important roles for regulating cell survival or apoptosis in tumorigenesis.

25 Three members of the Akt/PKB subfamily of second-messenger regulated serine/threonine protein kinases have been identified and termed Akt1/ PKB $\alpha$ , Akt2/PKB $\beta$ , and Akt3/PKB $\gamma$  respectively. The isoforms are homologous, particularly in regions encoding the catalytic domains. Akt/PKBs are activated by phosphorylation events occurring in response to PI3K signaling. PI3K  
 30 phosphorylates membrane inositol phospholipids, generating the second messengers phosphatidyl- inositol 3,4,5-trisphosphate and phosphatidylinositol 3,4-bisphosphate, which have been shown to bind to the PH domain of Akt/PKB. The current model of Akt/PKB activation proposes recruitment of the enzyme to the membrane by 3'-phosphorylated phosphoinositides, where phosphorylation of the  
 35 regulatory sites of Akt/PKB by the upstream kinases occurs (B.A. Hemmings, *Science* 275:628-630 (1997); B.A. Hemmings, *Science* 276:534 (1997); J. Downward, *Science* 279:673-674 (1998)).

Phosphorylation of Akt1/PKB $\alpha$  occurs on two regulatory sites, Thr<sup>308</sup> in the catalytic domain activation loop and on Ser<sup>473</sup> near the carboxy terminus (D. R. Alessi *et al.* *EMBO J.* 15:6541-6551 (1996) and R. Meier *et al.* *J. Biol. Chem.* 272:30491-30497 (1997)). Equivalent regulatory phosphorylation sites occur in  
 5 Akt2/PKB $\beta$  and Akt3/PKB $\gamma$ . The upstream kinase, which phosphorylates Akt/PKB at the activation loop site has been cloned and termed 3'-phosphoinositide dependent protein kinase 1 (PDK1). PDK1 phosphorylates not only Akt/PKB, but also p70 ribosomal S6 kinase, p90RSK, serum and glucocorticoid-regulated kinase (SGK), and protein kinase C. The upstream kinase phosphorylating the regulatory  
 10 site of Akt/PKB near the carboxy terminus has not been identified yet, but recent reports imply a role for the integrin-linked kinase (ILK-1), a serine/threonine protein kinase, or autophosphorylation.

Inhibition of Akt activation and activity can be achieved by inhibiting PI3K with inhibitors such as LY294002 and wortmannin. However, PI3K inhibition has  
 15 the potential to indiscriminately affect not just all three Akt isozymes but also other PH domain-containing signaling molecules that are dependent on PtdIns(3,4,5)-P3, such as the Tec family of tyrosine kinases. Furthermore, it has been disclosed that Akt can be activated by growth signals that are independent of PI3K.

Alternatively, Akt activity can be inhibited by blocking the activity of the  
 20 upstream kinase PDK1. No specific PDK1 inhibitors have been disclosed. Again, inhibition of PDK1 would result in inhibition of multiple protein kinases whose activities depend on PDK1, such as atypical PKC isoforms, SGK, and S6 kinases (Williams *et al.* *Curr. Biol.* 10:439-448 (2000)).

It is an object of the instant invention to provide novel compounds that are  
 25 inhibitors of Akt/PKB.

It is also an object of the present invention to provide pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

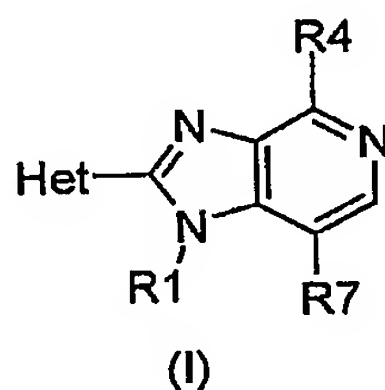
It is also an object of the present invention to provide a method for treating  
 30 cancer that comprises administering such inhibitors of Akt/PKB activity.

It is also an object of the present invention to provide a method for treating arthritis that comprises administering such inhibitors of Akt/PKB activity.

35

# SUMMARY OF THE INVENTION

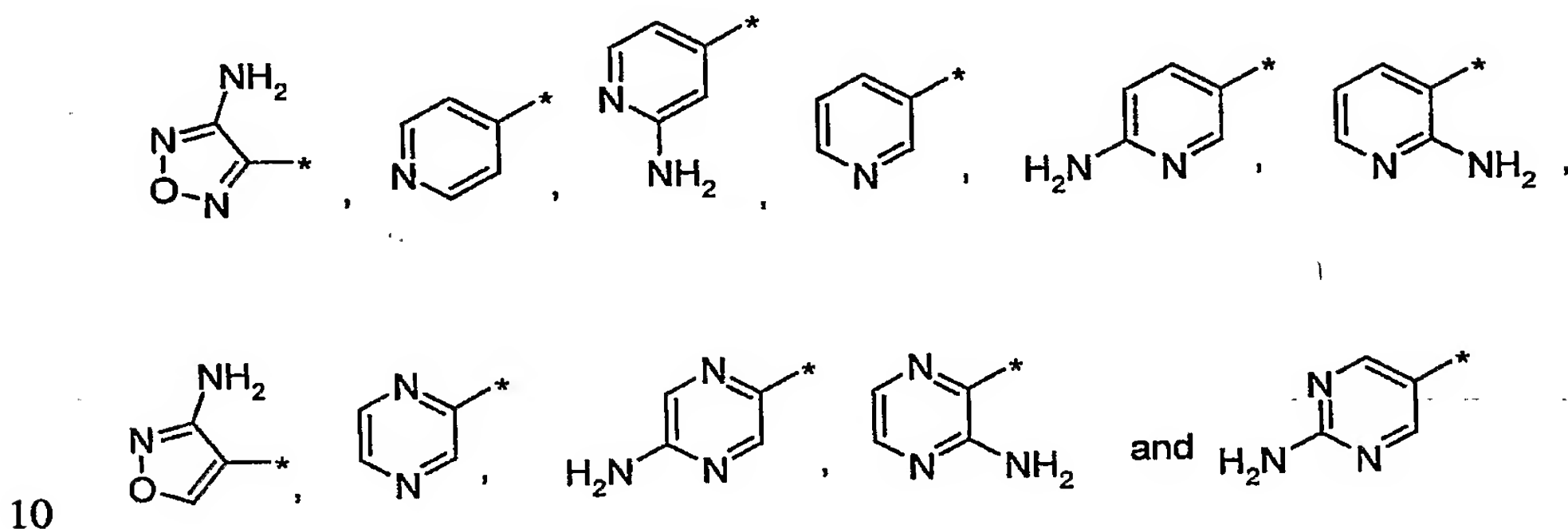
This invention relates to compounds of Formula (I):



5

wherein:

Het is selected from the group consisting of:



10

R<sup>1</sup> is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C<sub>1</sub>-C<sub>12</sub>aryl and C<sub>1</sub>-C<sub>12</sub>aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

15

20

R<sup>4</sup> is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally

25

containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen,  $-C(O)OR^2$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2NR^5R^6$ ,  $-S(O)_nR^2$  and protected  $-OH$ , where  $n$  is 0-2,

$R^2$  is hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $R^5$  and  $R^6$  are independently hydrogen, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ , or  $R^5$  and  $R^6$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2; and

$R^7$  is selected from hydrogen,  $-C(O)NR^9R^{10}$ ,  $-(CH_2)_nNR^9R^{10}$ ,  $-SO_2NR^9R^{10}$  and  $-(CH_2)_nOR^8$ , where  $n$  is 0-2;

$R^8$  is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ ,



where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2,

5  $R^9$  and  $R^{10}$  are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, - $C(O)OR^2$ , - $S(O)_nR^2$ , - $C(O)NR^2R^3$ , - $S(O)_2NR^2R^3$ , - $NR^2R^3$ , nitro, cyano,  
10 cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,  
or  $R^9$  and  $R^{10}$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is  
15 optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2;

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and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

25 This invention relates to a method of treating cancer, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

30 This invention relates to a method of treating arthritis, which comprises administering to a subject in need thereof an effective amount of an Akt/PKB inhibiting compound of Formula (I).

30

The present invention also relates to the discovery that the compounds of Formula (I) are active as inhibitors of Akt/PKB.

35 In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented Akt/PKB inhibiting compounds.

Included in the present invention are pharmaceutical compositions that comprise a pharmaceutical carrier and compounds useful in the methods of the invention.

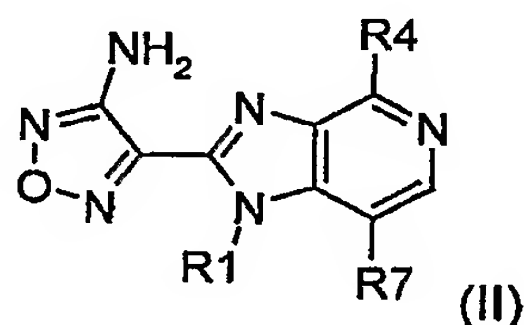
5 Also included in the present invention are methods of co-administering the presently invented Akt/PKB inhibiting compounds with further active ingredients.

# DETAILED DESCRIPTION OF THE INVENTION

10 This invention relates to compounds of Formula (I) as described above.  
The presently invented compounds of Formula (I) inhibit Akt/PKB activity. In particular, the compounds disclosed selectively inhibit one, two or the three Akt/PKB isoforms.

Included among the presently invented compounds of Formula (I) are those having Formula (II):

15



wherein:

20 R<sup>1</sup> is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1  
25 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C<sub>1</sub>-C<sub>12</sub>aryl and C<sub>1</sub>-C<sub>12</sub>aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

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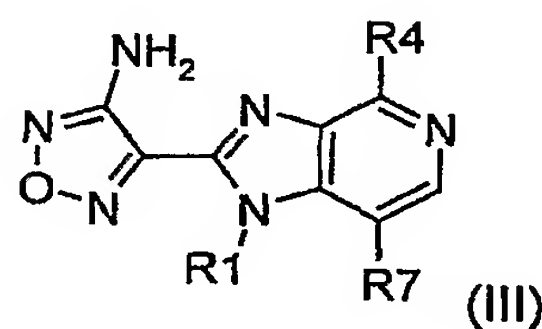
R<sup>4</sup> is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of

carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR<sup>2</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>n</sub>R<sup>2</sup> and protected -OH, where n is 0-2, R<sup>2</sup> is hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl, and R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted cycloalkyl, substituted C<sub>1</sub>-C<sub>12</sub>aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR<sup>2</sup>, -S(O)<sub>n</sub>R<sup>2</sup>, -C(O)NR<sup>2</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH, or R<sup>5</sup> and R<sup>6</sup> taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino, where R<sup>2</sup> and R<sup>3</sup> are independently hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl, and n is 0-2; and R<sup>7</sup> is selected from hydrogen, -C(O)NR<sup>9</sup>R<sup>10</sup>, -(CH<sub>2</sub>)<sub>n</sub>NR<sup>9</sup>R<sup>10</sup>, -SO<sub>2</sub>NR<sup>9</sup>R<sup>10</sup> and -(CH<sub>2</sub>)<sub>n</sub>OR<sup>8</sup>, where n is 0-2; R<sup>8</sup> is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR<sup>2</sup>, -S(O)<sub>n</sub>R<sup>2</sup>, -C(O)NR<sup>2</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH, where R<sup>2</sup> and R<sup>3</sup> are independently hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl, and n is 0-2,

5  $R^9$  and  $R^{10}$  are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, - $C(O)OR^2$ , - $S(O)_nR^2$ , - $C(O)NR^2R^3$ , - $S(O)_2NR^2R^3$ , - $NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,  
 10 or  $R^9$  and  $R^{10}$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,  
 15 where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and n is 0-2;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

20 Included among the presently invented compounds of Formula (I) are those having Formula (III):



wherein:

25  $R^1$  is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen,  
 30 cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen,  $C_1$ - $C_{12}$ aryl and  $C_1$ - $C_{12}$ aryl substituted with one or more



substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

5  $R^4$  is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen,  $-C(O)OR^2$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2NR^5R^6$ ,  $-S(O)_nR^2$  and protected  $-OH$ ,  
10 where n is 0-2,  
15  $R^2$  is hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  
20  $R^5$  and  $R^6$  are independently hydrogen, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ , or  $R^5$  and  $R^6$  taken together with the nitrogen to which they are attached  
25 represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,  
30 where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and n is 0-2; and

35  $R^7$  is selected from  $-C(O)NR^9R^{10}$ ,  $-(CH_2)_nNR^9R^{10}$ ,  $-SO_2NR^9R^{10}$  and  $-(CH_2)_nOR^8$ ,  
where n is 0-2;  
 $R^8$  is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one

or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ ,

5 where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2,

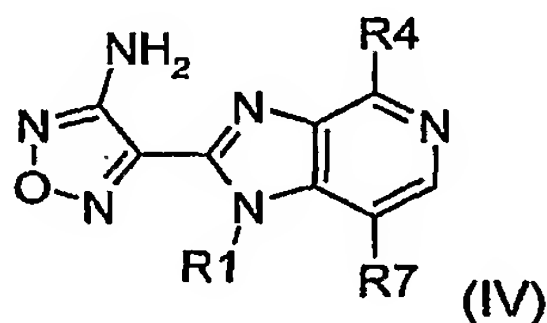
$R^9$  and  $R^{10}$  are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ ,  $-NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ ,

15 or  $R^9$  and  $R^{10}$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

20 where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2;

25 and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (I) are those having Formula (IV):



30 wherein:

$R^1$  is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy,

amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C<sub>1</sub>-C<sub>12</sub>aryl and C<sub>1</sub>-C<sub>12</sub>aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R<sup>4</sup> is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR<sup>2</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>n</sub>R<sup>2</sup> and protected -OH, where n is 0-2,

R<sup>2</sup> is hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl, and

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted cycloalkyl, substituted C<sub>1</sub>-C<sub>12</sub>aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR<sup>2</sup>, -S(O)<sub>n</sub>R<sup>2</sup>, -C(O)NR<sup>2</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH, or R<sup>5</sup> and R<sup>6</sup> taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2; and

5  $R^7$  is hydrogen;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

10 Included among the presently invented compounds of Formula (II) are those in which:

15  $R^1$  is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and  $C_1$ - $C_{12}$ aryl;

20  $R^4$  is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl and  $C_1$ - $C_{12}$ aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

25  $R^7$  is selected from hydrogen,  $-C(O)NR^9R^{10}$  and  $-(CH_2)_nOR^8$ , where  $n$  is 0-2;  
 $R^8$  is alkyl, piperidine, imidazolidine, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, hydroxy, nitro, cyano, cycloalkyl, halogen and  $C_1$ - $C_{12}$ aryl,  
 30  $R^9$  and  $R^{10}$  are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -  
 35  $NR^2R^3$ , nitro, cyano, cycloalkyl, halogen, aryl and substituted aryl, or  $R^9$  and  $R^{10}$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is



optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (III) are those in which:

$R^1$  is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and  $C_1$ - $C_{12}$ aryl;

$R^4$  is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl and  $C_1$ - $C_{12}$ aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

$R^7$  is selected from  $-C(O)NR^9R^{10}$  and  $-(CH_2)_nOR^8$ , where n is 0-2;

$R^8$  is alkyl, piperidine, imidazolidine, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, hydroxy, nitro, cyano, cycloalkyl, halogen and  $C_1$ - $C_{12}$ aryl,

$R^9$  and  $R^{10}$  are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl,  $-NR^2R^3$ , nitro, cyano, cycloalkyl, halogen, aryl and substituted aryl, or  $R^9$  and  $R^{10}$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is

optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R<sup>2</sup> and R<sup>3</sup> are independently hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the presently invented compounds of Formula (IV) are those in which:

R<sup>1</sup> is selected from: alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl containing from 1 to 3 heteroatoms and C<sub>1</sub>-C<sub>12</sub>aryl;

R<sup>4</sup> is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C<sub>1</sub>-C<sub>12</sub>aryl and C<sub>1</sub>-C<sub>12</sub>aryl substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryloxy, hydroxy, alkoxy, acyloxy, amino, N-acylamino, nitro, cyano and halogen; and

R<sup>7</sup> is hydrogen;

and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Included among the compounds useful in the present invention are:

- 4-(4-Phenyl-1-piperidin-4-yl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine;
- 4-[4-(3-Chloro-phenyl)-1-piperidin-4-yl-1H-imidazo-[4,5-c]pyridin-2-yl]furazan-3-ylamine;
- 4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;
- 4-[1-(cyclopropylmethyl)-4-(2-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 4-[4-(2-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

- 4-[1-(3-Amino-2,2-dimethylpropyl)-4-phenyl-1H-imidazo[4,5-c]pyridinyl-2-yl]-  
furazan-3-ylamine;
- 4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-  
oxadiazol-3-amine;
- 5 4-[4-chloro-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-  
amine;
- 4-[1-(cyclopropylmethyl)-4-(3-furanyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-  
oxadiazol-3-amine;
- 4-[1-(5-aminopentyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-  
amine;
- 10 4-[1-(6-aminohexyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-  
amine;
- 4-[1-(5-aminopentyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-  
oxadiazol-3-amine;
- 15 4-[1-(6-aminohexyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-  
oxadiazol-3-amine;
- 4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-methoxyphenyl)-1H-imidazo[4,5-c]pyridinyl-  
2-yl]-furazan-3-ylamine;
- 4-[1-(5-aminopentyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-  
amine;
- 20 4-[1-(6-aminohexyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-  
amine;
- 25 4-[4-phenyl-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-  
amine;
- 4-[4-(3-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-  
oxadiazol-3-amine;
- 4-[4-(4-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-  
oxadiazol-3-amine;
- 30 4-[1-(3-aminopropyl)-4-(2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-  
amine;
- 4-[1-(3-aminopropyl)-4-(1-piperidinyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-  
oxadiazol-3-amine;
- 35

- 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;  
 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-thiophen-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;  
 5 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;  
 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;  
 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-furan-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;  
 10 1-[2-(4-Amino-furazan-3-yl)-4-chloro-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;  
 1-[2-(4-Amino-furazan-3-yl)-4-(1H-pyrrol-2-yl))-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;  
 15 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;  
 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;  
 1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-furan-2-yl-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;  
 20 2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;  
 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;  
 25 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2,3-dichloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;  
 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;  
 2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;  
 30 2-(4-Amino-furazan-3-yl)-4-(3-chloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;  
 2-(4-Amino-furazan-3-yl)-4-phenyl-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;  
 35 2-(4-Amino-furazan-3-yl)-4-(5-chloro-thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;



- 2-(4-Amino-furazan-3-yl)-4-(2-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(3-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 5 2-(4-Amino-furazan-3-yl)-4-(3-bromo-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(1-naphthalenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 10 2-(4-Amino-furazan-3-yl)-4-(thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(3,4-methylenedioxyphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 2-(4-Amino-furazan-3-yl)-4-(3,5-dichloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;
- 15 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-biphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,4-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 20 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(phenylethynyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;
- 25 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- (2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenyl)methanol;
- 2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}-4-chlorophenol;
- 30 4-(1-ethyl-7-[[3-(methylamino)-1-pyrrolidinyl]carbonyl]-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;
- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(4-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;
- 35 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,5-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

- 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(1-benzothien-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;  
 4-[1-ethyl-4-phenyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;  
 5 4-{7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl}-1,2,5-oxadiazol-3-amine;  
 4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;  
 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;  
 10 4-[4-(3-chlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;  
 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-{2-[(phenylmethyl)amino]ethyl}-1H-imidazo[4,5-c]pyridine-7-carboxamide;  
 15 4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine  
 3-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;  
 4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}benzonitrile;  
 20 1-[2-(4-Amino-furazan-3-yl)-4-phenyl-1-piperidin-4yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;  
 4-(4-(3-chlorophenyl)-1-ethyl-7-[[3-(methylamino)-1-pyrrolidinyl]carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;  
 4-(4-(2,5-dichlorophenyl)-1-ethyl-7-[[3-(methylamino)-1-pyrrolidinyl]carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;  
 25 4-[4-(2,5-dichlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine; and  
 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylamino)propyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide;  
 30 and pharmaceutically acceptable salts, hydrates, solvates and esters thereof.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention.

By the term "protected hydroxy" or "protected -OH" as used herein, is meant  
 35 the alcoholic or carboxylic-OH groups which can be protected by conventional blocking groups in the art such as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York.

Compounds containing protected hydroxy groups may also be useful as intermediates in the preparation of the pharmaceutically active compounds of the invention.

By the term "aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 1 to 14 carbon atoms and optionally containing from one to five heteroatoms, provided that when the number of carbon atoms is 1 the aromatic ring contains at least four heteroatoms, when the number of carbon atoms is 2 the aromatic ring contains at least three heteroatoms, when the number of carbons is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom.

By the term "C<sub>1</sub>-C<sub>12</sub>aryl" as used herein, unless otherwise defined, is meant phenyl, naphthalene, 3,4-methylenedioxyphenyl, pyridine, biphenyl, quinoline, pyrimidine, quinazoline, thiophene, furan, pyrrole, pyrazole, imidazole benzothiohene and tetrazole.

The term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: -CO<sub>2</sub>R<sup>20</sup>, aryl, -C(O)NHS(O)<sub>2</sub>R<sup>20</sup>, -NHS(O)<sub>2</sub>R<sup>20</sup>, hydroxyalkyl, alkoxy, -C(O)NR<sup>21</sup>R<sup>22</sup>, acyloxy, alkyl, amino, methylamino, dimethylamino, N-acylamino, hydroxy, -(CH<sub>2</sub>)<sub>g</sub>C(O)OR<sup>23</sup>, -S(O)<sub>n</sub>R<sup>23</sup>, nitro, tetrazole, cyano, oxo, halogen, trifluoromethyl and protected -OH, where g is 0-6, R<sup>23</sup> is hydrogen or alkyl, R<sup>20</sup> is selected from hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl, aryl and trifluoromethyl, and R<sup>21</sup> and R<sup>22</sup> are independently selected from hydrogen, C<sub>1</sub>-C<sub>4</sub>alkyl, aryl and trifluoromethyl, and n is 0-2.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including -OCH<sub>3</sub> and -OC(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C<sub>3</sub>-C<sub>12</sub>.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl, cyclopropyl and cyclopentyl.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -OC(O)CH<sub>3</sub>, -OC(O)CH(CH<sub>3</sub>)<sub>2</sub> and -OC(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>.

By the term "N-acylamino" as used herein is meant -N(H)C(O)alkyl, where alkyl is as described herein. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH<sub>3</sub>, -N(H)C(O)CH(CH<sub>3</sub>)<sub>2</sub> and -N(H)C(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>.

By the term "aryloxy" as used herein is meant -Oaryl where aryl is phenyl, naphthyl, 3,4-methylenedioxyphenyl, pyridyl or biphenyl optionally substituted with one or more substituents selected from the group consisting of: alkyl, hydroxyalkyl, alkoxy, trifluoromethyl, acyloxy, amino, N-acylamino, hydroxy, -(CH<sub>2</sub>)<sub>g</sub>C(O)OR<sup>25</sup>, -S(O)<sub>n</sub>R<sup>25</sup>, nitro, cyano, halogen and protected -OH, where g is 0-6, R<sup>25</sup> is hydrogen or alkyl, and n is 0-2. Examples of aryloxy substituents as used herein include: phenoxy, 4-fluorophenyloxy and biphenyloxy.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain, and unless otherwise defined, the carbon chain will contain from 1 to 12 carbon atoms. Examples of alkyl substituents as used herein include: -CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub>, -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>3</sub>, -CH=CH<sub>2</sub>, and -C≡C-CH<sub>3</sub>.

By the term "treating" and derivatives thereof as used herein, is meant prophylactic and therapeutic therapy.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

Compounds of Formula (I) are included in the pharmaceutical compositions of the invention and used in the methods of the invention. Where a -COOH or -OH group is present, pharmaceutically acceptable esters can be employed, for example methyl, ethyl, pivaloyloxymethyl, and the like for -COOH, and acetate maleate and the like for -OH, and those esters known in the art for modifying solubility or hydrolysis characteristics, for use as sustained release or prodrug formulations.

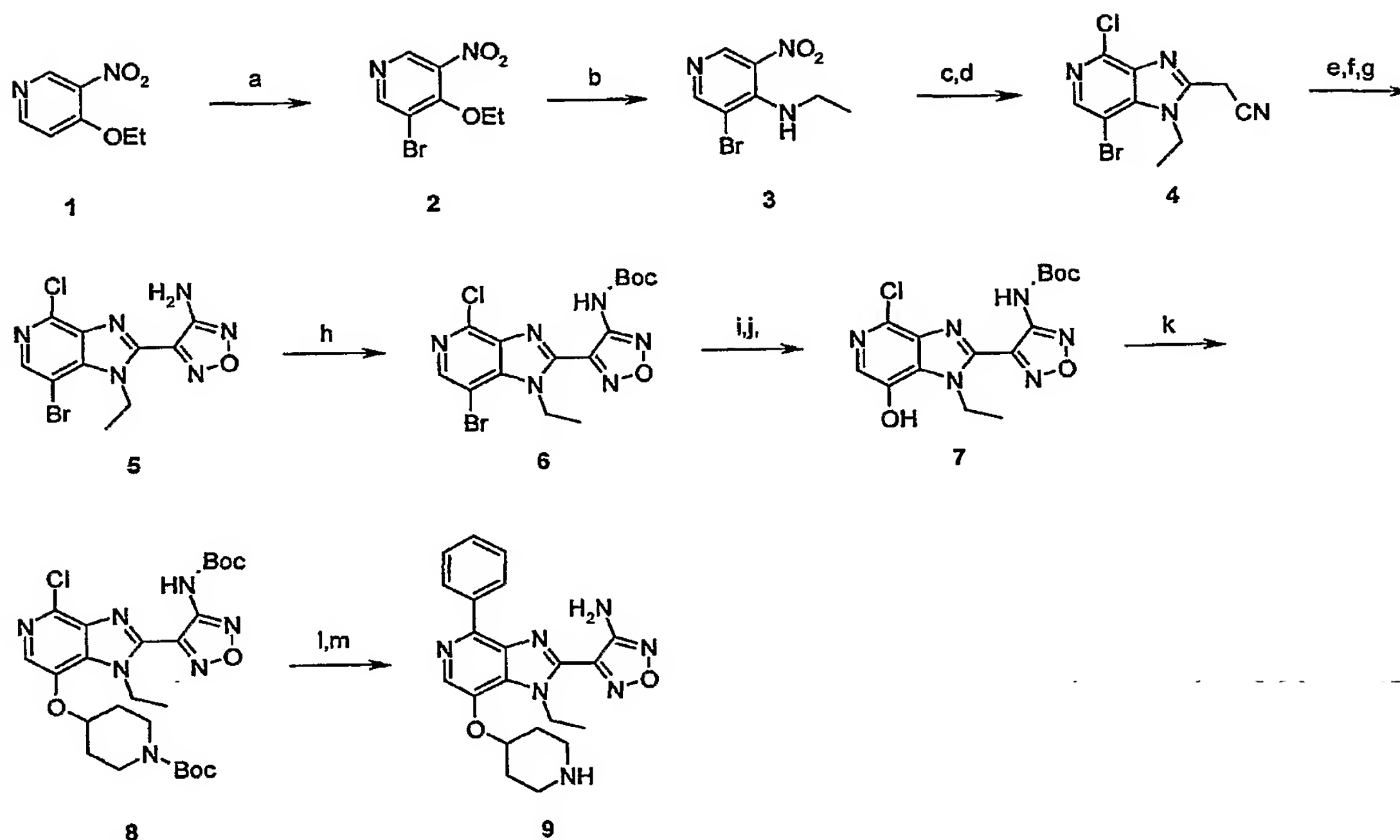
The novel compounds of Formulas I, II, III and IV are prepared as shown in Schemes I to III below, or by analogous methods, wherein the 'Het' and 'R' substituents are as defined in Formulas I, II, III and IV respectively and provided that the 'Het' and 'R' substituents do not include any such substituents that render inoperative the processes of Schemes I to IV. All of the starting materials are



commercially available or are readily made from commercially available starting materials by those of skill in the art.

5

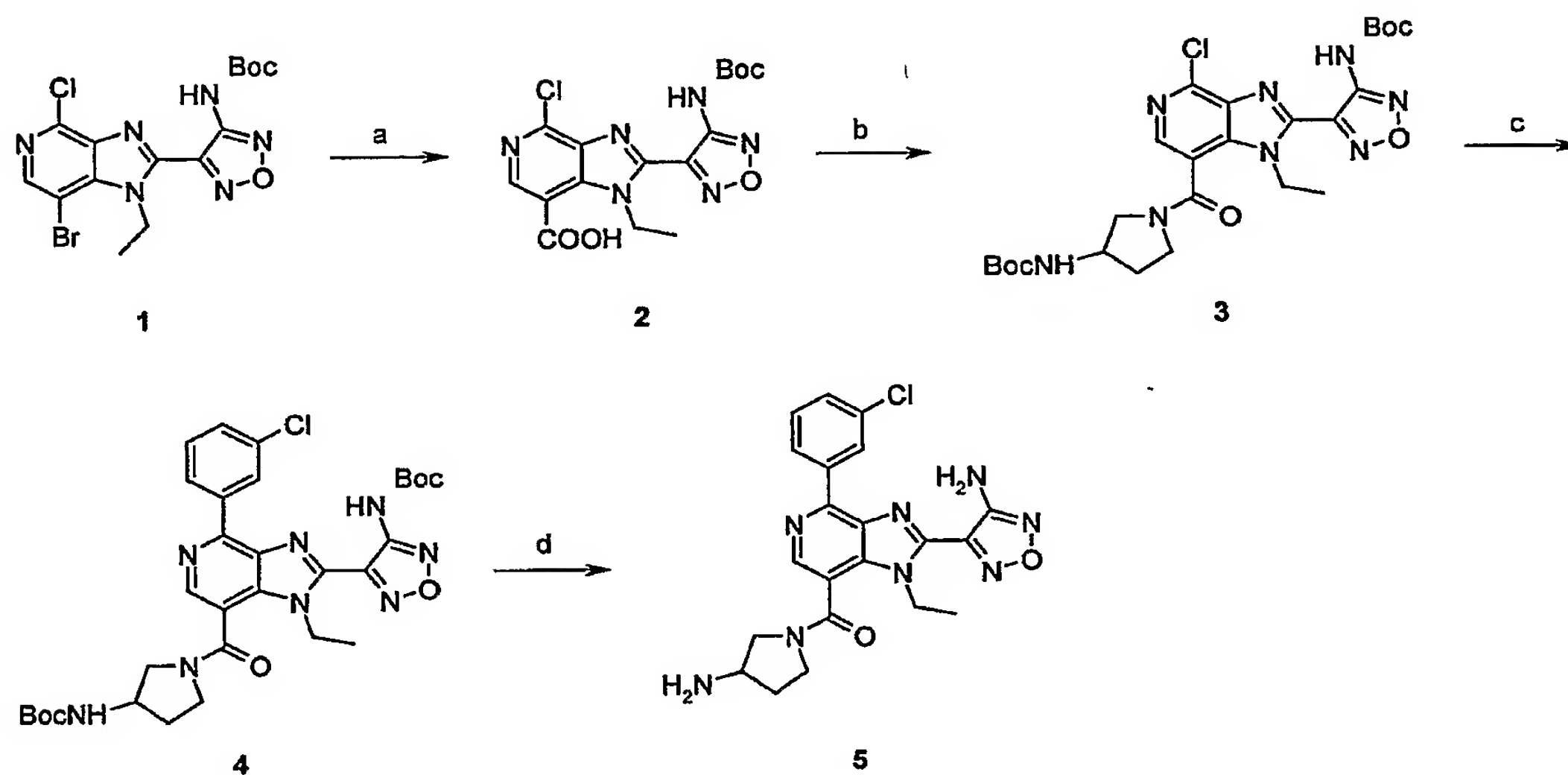
**SCHEME 1**



- 10 (a)  $\text{Br}_2$ , NaOAc, AcOH, 60 °C; (b)  $\text{EtNH}_2$ ; (c)  $\text{SnCl}_2$ , HCl; (d) ethyl cyanoacetate, 190 °C; (e)  $\text{NaNO}_2$ , HCl; (f)  $\text{NH}_2\text{OH}$ ; (g)  $\text{Et}_3\text{N}$ , dioxane, 150 °C; (h) di-*t*-butyldicarbonate, DMAP, pyridine; (i) i -  $n\text{-BuLi}$ , -78 °C. ii -  $\text{B(OMe)}_3$ ; (j)  $\text{H}_2\text{O}_2$ , NaOH; (k) 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate, polymer-bound  $\text{Ph}_3\text{P}$ , DEAD,  $\text{CH}_2\text{Cl}_2/\text{THF}$ ; (l)  $\text{PhB(OH)}_2$ ,  $(\text{Ph}_3\text{P})_4\text{Pd}$ , 2M  $\text{Na}_2\text{CO}_3$ , toluene/EtOH;
- 15 (m) TFA,  $\text{CH}_2\text{Cl}_2$ .

20

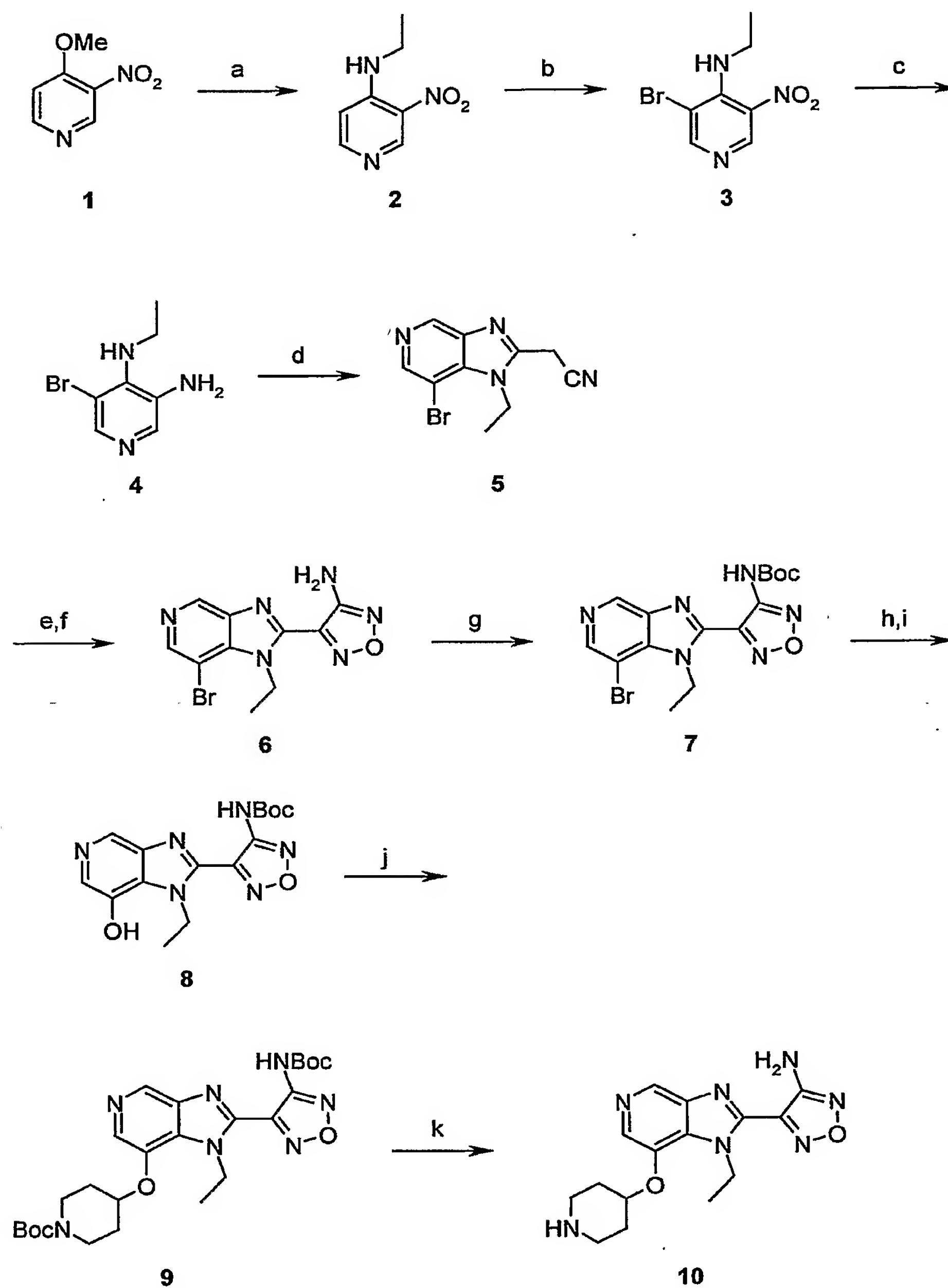
**SCHEME 2**



5

(a) i -  $n\text{-BuLi}$ , ii -  $\text{CO}_2$ ; (b) 1,1-dimethylethyl 3-pyrrolidinylcarbamate, EDCI, HOAt, NMM; (c)  $(3\text{-chlorophenyl})\text{B}(\text{OH})_2$ ,  $(\text{Ph}_3\text{P})_4\text{Pd}$ ,  $2\text{M Na}_2\text{CO}_3$ , toluene; (d) TFA.

## SCHEME 3



- 5 (a) EtNH<sub>2</sub>; (b) Br<sub>2</sub>, NaOAc, AcOH; (c) Fe powder, AcOH; (d) ethyl cyanoacetate, 190 °C; (e) NaNO<sub>2</sub>; (f) NH<sub>2</sub>OH; (g) di-*t*-butyldicarbonate, DMAP, pyridine; (h) i -

n-BuLi, ii - B(OMe)<sub>3</sub>; (i) H<sub>2</sub>O<sub>2</sub>, NaOH; (j) 1,1-dimethylethyl 4-hydroxy-1-piperidinecarboxylate, polymer-bound Ph<sub>3</sub>P, DEAD, CH<sub>2</sub>Cl<sub>2</sub>; (k) TFA.

By the term "co-administering" and derivatives thereof as used herein is meant either simultaneous administration or any manner of separate sequential administration of an AKT inhibiting compound, as described herein, and a further active ingredient or ingredients, known to be useful in the treatment of cancer, including chemotherapy and radiation treatment, or to be useful in the treatment of arthritis. The term further active ingredient or ingredients, as used herein, includes any compound or therapeutic agent known to or that demonstrates advantageous properties when administered to a patient in need of treatment for cancer or arthritis. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Examples of a further active ingredient or ingredients for use in combination with the presently invented Akt inhibiting compounds are chemotherapeutic agents.

Because the pharmaceutically active compounds of the present invention are active as Akt inhibitors they exhibit therapeutic utility in treating cancer and arthritis.

Compounds of the invention are tested for potency as Akt inhibitors by known methods, such as described in International Application No. PCT/US02/10880.

The pharmaceutically active compounds within the scope of this invention are useful as Akt inhibitors in mammals, particularly humans, in need thereof.

The present invention therefore provides a method of treating cancer, arthritis and other conditions requiring Akt inhibition, which comprises administering an effective compound of Formula (I) or a pharmaceutically acceptable salt, hydrate, solvate or ester thereof. The compounds of Formula (I) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as Akt inhibitors. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutically active compounds of the present invention are incorporated into convenient dosage forms such as capsules, tablets, or injectable preparations. Solid or liquid pharmaceutical carriers are employed. Solid carriers include, starch, lactose, calcium sulfate dihydrate, terra alba, sucrose, talc, gelatin, agar, pectin, acacia, magnesium stearate, and stearic acid;. Liquid carriers include syrup, peanut oil, olive oil, saline, and water. Similarly, the carrier or diluent may include any prolonged release material, such as glyceryl monostearate or glyceryl distearate, alone or with a wax. The amount of solid carrier varies widely but, preferably, will be from about 25 mg to about 1 g per dosage unit. When a liquid carrier is used, the preparation will be in the form of a syrup, elixir, emulsion, soft gelatin capsule, sterile injectable liquid such as an ampoule, or an aqueous or nonaqueous liquid suspension.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of an Akt inhibitor, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular Akt inhibitor in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing Akt inhibitory activity in mammals, including humans, comprises administering to a subject in need of such activity an effective Akt inhibiting amount of a pharmaceutically active compound of the present invention.



The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use as an Akt inhibitor.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in therapy.

5 The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating cancer.

The invention also provides for the use of a compound of Formula (I) in the manufacture of a medicament for use in treating arthritis.

10 The invention also provides for a pharmaceutical composition for use as an Akt inhibitor which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of cancer which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

15 The invention also provides for a pharmaceutical composition for use in treating arthritis which comprises a compound of Formula (I) and a pharmaceutically acceptable carrier.

No unacceptable toxicological effects are expected when compounds of the invention are administered in accordance with the present invention.

20 In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to treat cancer or arthritis, or compounds known to have utility when used in combination with an Akt inhibitor.

25 Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

### 30 Experimental Details

The compounds of Examples 1 to 72 are readily made according to Schemes I to III or by analogous methods.

### 35 Example 1

4-(4-Phenyl-1-piperidin-4-yl-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine;

Example 2

5 4-[4-(3-Chloro-phenyl)-1-piperidin-4-yl]-1H-imidazo-[4,5-c]pyridin-2-yl]furazan-3-ylamine;

Example 3

10 4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;

Example 4

15 4-[1-(cyclopropylmethyl)-4-(2-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 5

20 4-[4-(2-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 6

25 4-[1-(3-Amino-2,2-dimethylpropyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;

Example 7

30 4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 8

35 4-[4-chloro-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 9

4-[1-(cyclopropylmethyl)-4-(3-furanyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

5

Example 10

4-[1-(5-aminopentyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

10

Example 11

4-[1-(6-aminohexyl)-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 12

4-[1-(5-aminopentyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 13

4-[1-(6-aminohexyl)-4-(3-chlorophenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

25

Example 14

4-[1-(3-Amino-2,2-dimethylpropyl)-4-(3-methoxyphenyl)-1H-imidazo[4,5-c]pyridinyl-2-yl]-furazan-3-ylamine;

30

Example 15

4-[1-(5-aminopentyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35

Example 16

4-[1-(6-aminoethyl)-4-(3-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

5

Example 17

4-[4-phenyl-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

10

Example 18

4-[4-(3-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 19

4-[4-(4-chlorophenyl)-1-(3-piperidinylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 20

4-[1-(3-aminopropyl)-4-(2-thienyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

25

Example 21

4-[1-(3-aminopropyl)-4-(1-piperidinyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

30

Example 22

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

35

Example 23

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-thiophen-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

5

Example 24

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

10

Example 25

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-pyridin-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

15

Example 26

1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-furan-3-yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone;

20

Example 27

1-[2-(4-Amino-furazan-3-yl)-4-chloro-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

25

Example 28

1-[2-(4-Amino-furazan-3-yl)-4-(1H-pyrrol-2-yl))-1-ethyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

30

Example 29

1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-methoxyphenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

35



Example 30

1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

5

Example 31

1-[2-(4-Amino-furazan-3-yl)-1-ethyl-4-furan-2-yl-1H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

10

Example 32

2-(4-Amino-furazan-3-yl)-1-ethyl-4-phenyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

15

Example 33

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(3-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

20

Example 34

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2,3-dichloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

25

Example 35

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-chloro-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

30

Example 36

2-(4-Amino-furazan-3-yl)-1-ethyl-4-(2-hydroxy-phenyl)-1H-imidazo[4,5-c]pyridine-7-carboxylic acid [1-(4-chloro-benzyl)-2-hydroxy-ethyl]-amide;

35

Example 37

2-(4-Amino-furazan-3-yl)-4-(3-chloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

5

Example 38

2-(4-Amino-furazan-3-yl)-4-phenyl-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

10

Example 39

2-(4-Amino-furazan-3-yl)-4-(5-chloro-thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

15

Example 40

2-(4-Amino-furazan-3-yl)-4-(2-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

20

Example 41

2-(4-Amino-furazan-3-yl)-4-(3-amino-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

25

Example 42

2-(4-Amino-furazan-3-yl)-4-(3-bromo-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

30

Example 43

2-(4-Amino-furazan-3-yl)-4-(1-naphthalenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

35

Example 44

2-(4-Amino-furazan-3-yl)-4-(thiophen-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

5

Example 45

2-(4-Amino-furazan-3-yl)-4-(3,4-methylenedioxyphenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

10

Example 46

2-(4-Amino-furazan-3-yl)-4-(3,5-dichloro-phenyl)-1-ethyl-1H-imidazo[4,5-c]pyridine-7-carboxylic acid pyrrolidin-3-ylamide;

15

Example 47

Preparation of 4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine, trifluoroacetate salt

20

a) Cyclopropylmethyl-(3-nitropyridin-4-yl)amine

4-Ethoxy-3-nitropyridine, hydrochloride (14.5 g, 70.8 mmol) in ethyl acetate was washed twice with 1N NaHCO<sub>3</sub>. The organic layer was dried over MgSO<sub>4</sub>, filtered and the solvent evaporated under reduced pressure to give 11.8 g of a light tan solid. The free-amine (11.8 g, 69.9 mmol) and cyclopropanemethylamine (5.00 g, 70.3 mmol) in EtOH were heated at 80 °C in a sealed tube for 12 h. After allowing to warm to RT, the solvent was removed under reduced pressure to give a yellow oil. Flash chromatography (silica gel, hexanes then hexanes/Et<sub>2</sub>O (1:1:1) then Et<sub>2</sub>O/CH<sub>2</sub>Cl<sub>2</sub> (1:1) then CH<sub>2</sub>Cl<sub>2</sub>) gave 13.1 g of the desired material. MS (ES) m/z 194.2 [M+H]<sup>+</sup>.

25

30

b) (3-Bromo-5-nitropyridin-4-yl)cyclopropylmethylamine

To the compound of Example 47(a) (13.1 g, 68.0 mmol) and NaOAc (25.1 g, 305.5 mmol) in glacial acetic acid (20 mL) was added bromine (15.6 g, 97.6 mmol). The reaction was maintained at 100 °C for 20 h. After cooling to room temperature, the mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub> and filtered. The solvent was

35

removed from the filtrate under reduced pressure and the residue purified by flash chromatography (silica gel, 0% to 20% EtOAc/hexanes) to give 9.81 g of the desired product as a yellow oil. MS (ES)  $m/z$  272.2  $[M+H]^+$ .

5 c) 5-Bromo-2-chloro-N<sup>4</sup>-cyclopropylmethylpyridine-3,4-diamine

The compound of Example 47(b) (3.11 g, 11.43 mmol) was dissolved into ethanol (25 mL) and cooled to 0 °C. Concentrated HCl (25 mL) was added while maintaining the reaction at 0 °C. After 15 min., tin (II) chloride (6.55 g, 34.5 mmol) was added. After 3 h at 0 °C, the reaction mixture was poured into a solution of  
10 NaOH (24 g, 600 mmol) in ice water (75 mL). The mixture was extracted with EtOAc and the combined organic extracts were dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure to give 3.05 g of the desired material. This was used without further purification. MS (ES)  $m/z$  276.0  $[M+H]^+$ .

15 d) [7-Bromo-4-chloro-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]acetonitrile

The compound of Example 47(c) (2.60 g, 9.40 mmol) in ethyl cyanoacetate (10.6 g, 93.8 mmol) was heated to 190 °C for 3 h. The reaction was allowed to cool to RT. Flash chromatography (silica gel, 50% Et<sub>2</sub>O/CHCl<sub>3</sub>) gave 1.62 g of the  
20 desired material. MS(ES)  $m/z$  325.0  $[M+H]^+$ .

e) (7-Bromo-4-chloro-1-cyclopropylmethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)hydroxyimino-acetonitrile

To the compound of Example 47(d) (1.32 g, 4.65 mmol) in MeOH (30 mL) and 2N HCl (15 mL) was added sodium nitrite (0.59 g, 8.55 mmol). After stirring at  
25 RT for 1 h, the precipitate was collected by filtration and dried under vacuum to give 1.35 g of the desired material as a yellow powder. This was used without further purification. MS (ES)  $m/z$  354.0  $[M+H]^+$ .

30 f) 2-(7-Bromo-4-chloro-1-cyclopropylmethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl)-*N*-hydroxy-2-hydroxyimino acetamidine

To the compound of Example 47(e) (1.35 g, 3.80 mmol) and Et<sub>3</sub>N (1.46 g, 14.4 mmol) in THF (20 mL) was added hydroxylamine (0.70 mL, 10.6 mmol). The reaction was heated at 90 °C for 1 h. After allowing to cool to RT, the reaction was  
35 diluted with EtOAc and washed with H<sub>2</sub>O and brine. The organic extract was dried over MgSO<sub>4</sub> and the solvent was removed under reduced pressure to give 1.56 g

of the desired material as a yellow oil. This was used without further purification.  
MS (ES)  $m/z$  387.0  $[M+H]^+$ .

5 g) 4-(7-Bromo-4-chloro-1-cyclopropylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-ylamine

The compound of Example 47(f) (1.57 g, 3.80 mmol) and Et<sub>3</sub>N (2.18 g, 21.5 mmol) in 1,4-dioxane was heated at 150 °C in a sealed tube for 1 h. After allowing to cool to RT, the crude reaction mixture purified by flash chromatography (silica gel, 0% to 20 % EtOAc/hexanes) to give 0.90 g of the desired product as a cream  
10 colored solid. MS (ES)  $m/z$  368.8  $[M+H]^+$ .

h) [4-(7-Bromo-4-chloro-1-cyclopropylmethyl-1H-imidazo[4,5-c]pyridin-2-yl)furazan-3-yl]di-*tert*-butoxycarbonylamine

To the compound of Example 47(g) (0.90 g, 2.43 mmol) in CHCl<sub>3</sub> (20 mL)  
15 was added di-*tert*-butyldicarbonate (1.12 g, 5.14 mmol) and dimethylaminopyridine (67.7 mg, 0.55 mmol). The reaction was heated to reflux for 1 h. After allowing to cool to RT, the solvent was removed under reduced pressure. Trituration from hot MeOH gave 1.06 g of the desired material as a white powder. MS (ES)  $m/z$  569.2  $[M+H]^+$ .

20

i) 4-Chloro-1-(cyclopropylmethyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,5-oxadiazol-3-yl]-1H-imidazo[4,5-c]pyridine-7-carboxylic acid

A solution of the compound of Example 47(h) (0.84 g, 1.48 mmol) in dry THF (25 mL) was degassed and then cooled to -78 °C. *n*-Butyllithium (1.50 mL of a  
25 2.50 M solution in hexanes, 3.75 mmol) was added to the cooled solution. After 5 minutes, CO<sub>2</sub> gas was bubbled into the reaction for 1 h while continuing to maintain the reaction at -78 °C. The reaction was allowed to reach ambient temperature and diluted with EtOAc. The organic layer was washed with 1N NaOH and dried over MgSO<sub>4</sub>. The solvent was removed under reduced pressure. Purification by  
30 preparative reverse phase HPLC (Phenomenex<sup>®</sup> Synergi MaxRP 80A column, gradient 10% AcCN/H<sub>2</sub>O to 80% AcCN/H<sub>2</sub>O + 0.1% TFA) gave 0.14 g of the desired material as a grey solid. MS(ES)  $m/z$  435.4  $[M+H]^+$ .

35 j) 1,1-Dimethylethyl [1-({4-chloro-1-(cyclopropylmethyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,5-oxadiazol-3-yl]-1H-imidazo[4,5-c]pyridin-7-yl}carbonyl)-3-pyrrolidinyl]carbamate



A solution of 3-(*tert*-butoxycarbonylamino)pyrrolidine (72.5 mg, 0.39 mmol) in CH<sub>2</sub>Cl<sub>2</sub> was added to a solution of the compound of Example 47(i) (0.11 g, 0.24 mmol) in CH<sub>2</sub>Cl<sub>2</sub>. 1-Hydroxy-7-azabenzotriazole (49.3 mg, 0.36 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (84.1 mg, 0.44 mol) and Et<sub>3</sub>N (145 mg, 1.44 mmol) were added sequentially. After 3 d at RT, the solvent was removed under reduced pressure. Flash chromatography (silica gel, 3% EtOH/CHCl<sub>3</sub>) gave the desired product. This was further purified by crystallization from Et<sub>2</sub>O/hexanes to give 0.11 g of the desired compound as a white solid. MS(ES) m/z 603.2 [M+H]<sup>+</sup>.

k) 4-[7-[(3-Amino-1-pyrrolidinyl)carbonyl]-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine, trifluoroacetate salt

To a degased mixture of the compound of Example 47(j) (39.2 mg, 0.06 mmol), 3-chlorophenylboronic acid (22.8 mg, 0.14 mmol) and 2.0M Na<sub>2</sub>CO<sub>3</sub> (0.20 mL, 0.40 mmol) in EtOH/toluene (1:1 v/v, 10 mL) was added (Ph<sub>3</sub>P)<sub>4</sub>Pd (13.5 mg). After 4 hours at 125 °C, the reaction was allowed to cool to room temperature, diluted with MeOH and filtered. The filtrate evaporated under reduced pressure and the resulting residue was dissolved in 4N HCl/dioxane. After 3.5 h the solvent was removed under reduced pressure and the residue dissolved in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and trifluoroacetic acid (5 mL). After 1 h, the solvent was removed under reduced pressure and the residue subjected to preparative reverse phase HPLC (Phenomenex<sup>®</sup> Synergi MaxRP 80A column, gradient 10% AcCN/H<sub>2</sub>O to 80% AcCN/H<sub>2</sub>O + 0.1% TFA) to give 15.2 mg of the title compound as a white powder. MS (ES) m/z 479.2 [M+H]<sup>+</sup>.

#### Example 48

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-biphenyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

#### Example 49

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,4-dichlorophenyl)-1-ethyl-1*H*-imidazo[4,5-*c*]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

Example 50

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(phenylethynyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

5

Example 51

2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

10

Example 52

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 53

(2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenyl)methanol;

20

Example 54

2-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}-4-chlorophenol;

25

Example 55

4-(1-ethyl-7-[[3-(methylamino)-1-pyrrolidinyl]carbonyl]-4-phenyl-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

30

Example 56

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-(4-methylphenyl)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35

Example 57

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(2,5-dichlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

5

Example 58

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(1-benzothien-2-yl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

10

Example 59

4-[1-ethyl-4-phenyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

15

Example 60

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-4-[4-(methyloxy)phenyl]-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

20

Example 61

4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

25

Example 62

4-[7-[(3-amino-1-pyrrolidinyl)carbonyl]-4-(4-chlorophenyl)-1-ethyl-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

30

Example 63

4-[4-(3-chlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35

Example 64

Preparation of 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-{2-[(phenylmethyl)amino]ethyl}-1H-imidazo[4,5-c]pyridine-7-carboxamide, trifluoroacetate salt

a) 4-(3-Chlorophenyl)-1-(cyclopropylmethyl)-2-[4-({[(1,1-dimethylethyl)oxy]carbonyl}amino)-1,2,5-oxadiazol-3-yl]-1H-imidazo[4,5-c]pyridine-7-carboxylic acid

10 To a solution of the compound of Example 47(i) (100 mg, 0.23 mmol) and 3-chlorophenylboronic acid (47.5 mg, 0.30 mmol) in EtOH (10 mL) and toluene (10 mL) was added 2M Na<sub>2</sub>CO<sub>3</sub> (0.70 mL, 1.40 mmol). The mixture was degased and (Ph<sub>3</sub>P)<sub>4</sub>Pd (48.1 mg.; 0.04 mmol) was added. The reaction was heated to reflux for 6 h. After allowing to cool to RT, the reaction mixture was filtered and the filtrate  
15 was concentrated. Flash chromatography (silica gel, 10% to 25% EtOH/CHCl<sub>3</sub>) gave 135 mg of the desired material as a white solid. MS (ES) m/z 511.4 [M+H]<sup>+</sup>.

b) 1,1-Dimethylethyl 4-{4-(3-chlorophenyl)-1-(cyclopropylmethyl)-7-[(2-[(phenylmethyl)amino]ethyl)amino]carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl}-1,2,5-oxadiazol-3-yl)carbamate

20 To the compound of Example 64(a) (37.2 mg, 0.073 mmol) in CH<sub>2</sub>Cl<sub>2</sub> and DMF was added N-benzylethylenediamine (20 mg, 0.13 mmol), 1-hydroxy-7-azabenzotriazole (17.5 mg, 0.13 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (27.8 mg, 0.15 mmol) and triethylamine (43.7 mg,  
25 0.43 mmol). After 6 d at RT, the solvent was removed under reduced pressure. Flash chromatography (silica gel, 5% MeOH/CHCl<sub>3</sub>) gave 27.4 mg of the desired material as a tan oil. MS (ES) m/z 643.4 [M+H]<sup>+</sup>.

c) 2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-{2-[(phenylmethyl)amino]ethyl}-1H-imidazo[4,5-c]pyridine-7-carboxamide, trifluoroacetate salt

30 The compound of Example 64(b) (27.4 mg) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) and trifluoroacetic acid (10 mL). After 1 h at RT, the solvent was removed under reduced pressure. Trituration with Et<sub>2</sub>O gave 13.8 mg of the title compound  
35 as a white powder. MS (ES) m/z 543.4 [M+H]<sup>+</sup>.

Example 65

4-[1-Ethyl-7-(piperidin-4-yloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-furazan-3-ylamine;

5

Example 66

3-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}phenol;

10

Example 67

4-{2-(4-amino-1,2,5-oxadiazol-3-yl)-7-[(3-amino-1-pyrrolidinyl)carbonyl]-1-ethyl-1H-imidazo[4,5-c]pyridin-4-yl}benzonitrile;

15

Example 68

1-[2-(4-Amino-furazan-3-yl)-4-phenyl-1-piperidin-4yl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-amino-pyrrolidin-1-yl)-methanone;

20

Example 69

4-(4-(3-chlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

25

Example 70

4-(4-(2,5-dichlorophenyl)-1-ethyl-7-{[3-(methylamino)-1-pyrrolidinyl]carbonyl}-1H-imidazo[4,5-c]pyridin-2-yl)-1,2,5-oxadiazol-3-amine;

30

Example 71

4-[4-(2,5-dichlorophenyl)-1-ethyl-7-(4-piperidinyloxy)-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-amine;

35



Example 72

Preparation of 2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylaminopropyl)-1H-imidazo[4,5-c]pyridine-7-carboxamide, trifluoroacetate salt

a) 1,1-Dimethylethyl {4-[4-(3-chlorophenyl)-1-(cyclopropylmethyl)-7-([3-(dimethylamino)propyl]amino)carbonyl]-1H-imidazo[4,5-c]pyridin-2-yl]-1,2,5-oxadiazol-3-yl}carbamate

To the compound of Example 64(a) (41.2 mg, 0.081 mmol) and 3-dimethylaminopropylamine (16.2 mg, 0.16 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (5 mL) and DMF (2 mL) was added 1-hydroxy-7-azabenzotriazole (17.0 mg, 0.12 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide, hydrochloride (28.6 mg, 0.15 mol) and Et<sub>3</sub>N (43.7 mg, 0.43 mmol). After 6 d at RT, the solvent was removed under reduced pressure. Preparative reverse phase HPLC (Phenomenex<sup>®</sup> Synergi MaxRP 80A column, gradient 10% AcCN/H<sub>2</sub>O to 80% AcCN/H<sub>2</sub>O + 0.1% TFA) gave 37.5 mg of the desired material as a clear oil. MS (ES) m/z 595.4 [M+H]<sup>+</sup>.

b) 2-(4-Amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylaminopropyl)-1H-imidazo[4,5-c]pyridine-7-carboxamide, trifluoroacetate

In a manner analogous to the preparation of the compound of Example 64(c), the compound of Example 72(a) (37.5 mg, 0.063 mmol) gave 12.6 mg of the title compound as a white powder following trituration from hexanes. MS (ES) m/z 496.4 [M+H]<sup>+</sup>.

Example 73- Capsule Composition

An oral dosage form for administering the present invention is produced by filling a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table I, below.

Table I

INGREDIENTS	AMOUNTS
4-(4-Phenyl-1-piperidin-4-yl)-1H-imidazo[4,5-c]pyridin-2-yl)-furazan-3-ylamine	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

Example 74 - Injectable Parenteral Composition

5 An injectable form for administering the present invention is produced by stirring 1.5% by weight of 1-[2-(4-Aminofurazan-3-yl)-1-ethyl-4-phenyl-1-H-imidazo[4,5-c]pyridin-7-yl]-1-(3-aminopyrrolidin-1-yl)methanone in 10% by volume propylene glycol in water.

Example 75 - Tablet Composition

10

The sucrose, calcium sulfate dihydrate and an Akt inhibitor as shown in Table II below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid; screened and compressed into a tablet.

15

Table II

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
2-(4-amino-1,2,5-oxadiazol-3-yl)-4-(3-chlorophenyl)-1-(cyclopropylmethyl)-N-[3-(dimethylamino)propyl]-1H-imidazo[4,5-c]pyridine-7-carboxamide	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

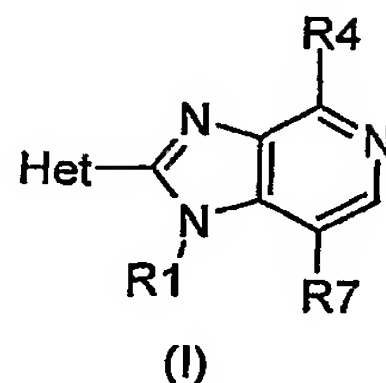
20

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound of Formula (I):

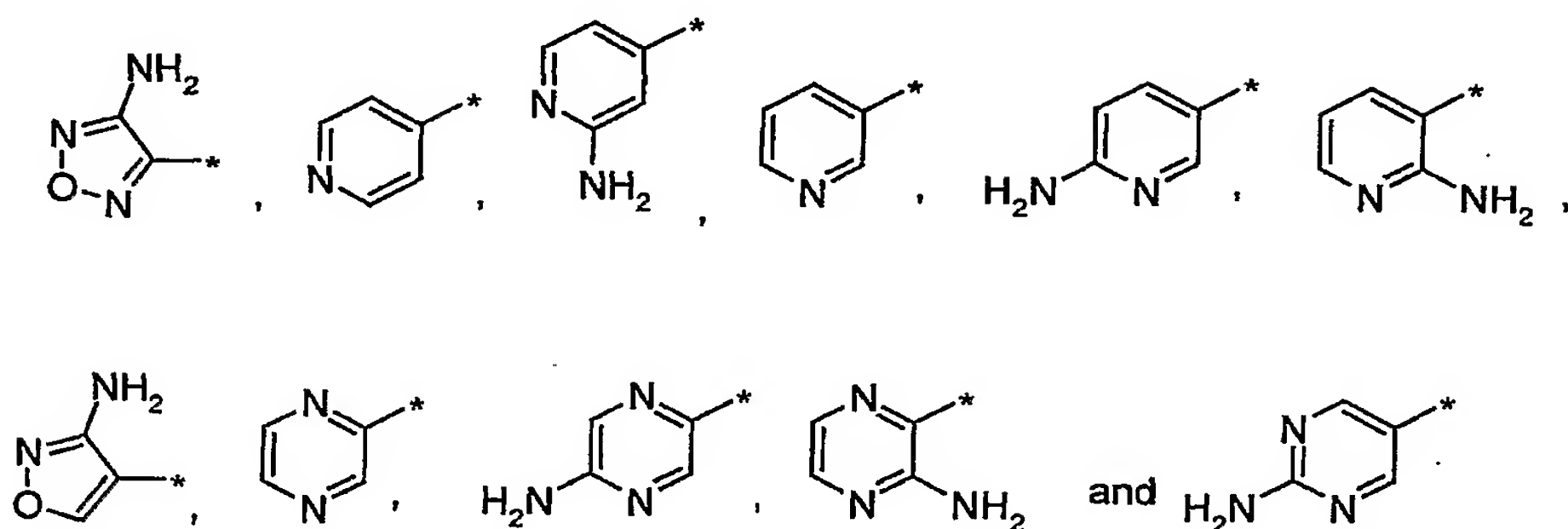
5



wherein:

Het is selected from the group consisting of:

10



15

R<sup>1</sup> is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C<sub>1</sub>-C<sub>12</sub>aryl and C<sub>1</sub>-C<sub>12</sub>aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

20

25

$R^4$  is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen,  $-C(O)OR^2$ ,  $-C(O)NR^5R^6$ ,  $-S(O)_2NR^5R^6$ ,  $-S(O)_nR^2$  and protected  $-OH$ , where  $n$  is 0-2,

$R^2$  is hydrogen, alkyl, cycloalkyl,  $C_1-C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1-C_{12}$ aryl, and

$R^5$  and  $R^6$  are independently hydrogen, cycloalkyl,  $C_1-C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1-C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ , or  $R^5$  and  $R^6$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1-C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1-C_{12}$ aryl, and  $n$  is 0-2; and

$R^7$  is selected from hydrogen,  $-C(O)NR^9R^{10}$ ,  $-(CH_2)_nNR^9R^{10}$ ,  $-SO_2NR^9R^{10}$  and  $-(CH_2)_nOR^8$ , where  $n$  is 0-2;

$R^8$  is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,

-C(O)NR<sup>2</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

where R<sup>2</sup> and R<sup>3</sup> are independently hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl, and n is 0-2,

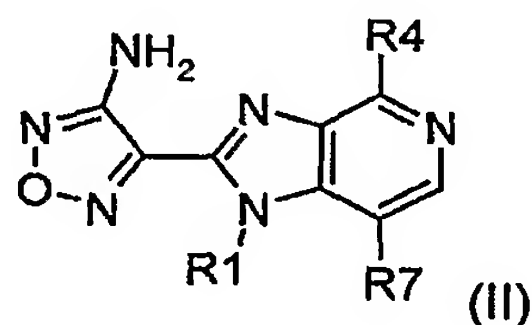
R<sup>9</sup> and R<sup>10</sup> are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, C<sub>1</sub>-C<sub>12</sub>aryl, substituted cycloalkyl, substituted C<sub>1</sub>-C<sub>12</sub>aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl, -C(O)OR<sup>2</sup>, -S(O)<sub>n</sub>R<sup>2</sup>, -C(O)NR<sup>2</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, -NR<sup>2</sup>R<sup>3</sup>, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH,

or R<sup>9</sup> and R<sup>10</sup> taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

where R<sup>2</sup> and R<sup>3</sup> are independently hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl, and n is 0-2.

2. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (I), as described in claim 1.

3. A compound of Claim 1 represented by the following Formula (II):



wherein:

R<sup>1</sup> is selected from: hydrogen, alkyl, alkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy,

amino, N-acylamino, cyclopropyl and halogen, cycloalkyl, cycloalkyl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, cycloalkyl containing from 1 to 3 heteroatoms, cycloalkyl containing from 1 to 3 heteroatoms substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen, C<sub>1</sub>-C<sub>12</sub>aryl and C<sub>1</sub>-C<sub>12</sub>aryl substituted with one or more substituents selected from the group consisting of: hydroxy, alkoxy, amino, N-acylamino and halogen;

R<sup>4</sup> is selected from hydrogen, halogen, alkyl, substituted alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, and a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and optionally containing one or more heteroatoms, provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and when the number of carbon atoms is 4 the aromatic ring contains at least one heteroatom, and optionally substituted with one or more substituents selected from the group consisting of: alkyl, substituted alkyl, aryl, substituted cycloalkyl, substituted aryl, aryloxy, oxo, hydroxy, alkoxy, cycloalkyl, acyloxy, amino, N-acylamino, nitro, cyano, halogen, -C(O)OR<sup>2</sup>, -C(O)NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>2</sub>NR<sup>5</sup>R<sup>6</sup>, -S(O)<sub>n</sub>R<sup>2</sup> and protected -OH, where n is 0-2,

R<sup>2</sup> is hydrogen, alkyl, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted alkyl, substituted cycloalkyl and substituted C<sub>1</sub>-C<sub>12</sub>aryl, and

R<sup>5</sup> and R<sup>6</sup> are independently hydrogen, cycloalkyl, C<sub>1</sub>-C<sub>12</sub>aryl, substituted cycloalkyl, substituted C<sub>1</sub>-C<sub>12</sub>aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, -C(O)OR<sup>2</sup>, -S(O)<sub>n</sub>R<sup>2</sup>, -C(O)NR<sup>2</sup>R<sup>3</sup>, -S(O)<sub>2</sub>NR<sup>2</sup>R<sup>3</sup>, nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected -OH, or R<sup>5</sup> and R<sup>6</sup> taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,



where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2; and

5  $R^7$  is selected from hydrogen,  $-C(O)NR^9R^{10}$ ,  $-(CH_2)_nNR^9R^{10}$ ,  $-SO_2NR^9R^{10}$  and  $-(CH_2)_nOR^8$ ,

where  $n$  is 0-2;

10  $R^8$  is alkyl, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms, piperidyl and pyrrolidinyl, each of which is optionally substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ ,

15 where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2,

20  $R^9$  and  $R^{10}$  are independently hydrogen, cycloalkyl, cycloalkyl containing from 1 to 3 heteroatoms,  $C_1$ - $C_{12}$ aryl, substituted cycloalkyl, substituted  $C_1$ - $C_{12}$ aryl, alkyl or alkyl substituted with one or more substituents selected from the group consisting of: alkoxy, acyloxy, aryloxy, amino, N-acylamino, oxo, hydroxy, methylamino, dimethylamino, hydroxyalkyl,  $-C(O)OR^2$ ,  $-S(O)_nR^2$ ,  $-C(O)NR^2R^3$ ,  $-S(O)_2NR^2R^3$ ,  $-NR^2R^3$ , nitro, cyano, cycloalkyl, substituted cycloalkyl, halogen, aryl, substituted aryl and protected  $-OH$ ,

25 or  $R^9$  and  $R^{10}$  taken together with the nitrogen to which they are attached represent a 5 to 6 member saturated ring containing up to one other heteroatom selected from oxygen and nitrogen, where the ring is optionally substituted with one or more substituents selected from amino, methylamino and dimethylamino,

30 where  $R^2$  and  $R^3$  are independently hydrogen, alkyl, cycloalkyl,  $C_1$ - $C_{12}$ aryl, substituted alkyl, substituted cycloalkyl and substituted  $C_1$ - $C_{12}$ aryl, and  $n$  is 0-2.

35 4. A pharmaceutically acceptable salt, hydrate, solvate or ester of a compound of Formula (II), as described in claim 3.

ABSTRACT OF THE DISCLOSURE

Invented are novel 1H-imidazo[4,5-c]pyridin-2-yl compounds, the use of such compounds as inhibitors of PKB/AKT kinase activity and in the treatment of cancer and arthritis.